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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,396	09/26/2003	Daniel V. Santi	300622010900	9173

81228 7590 09/17/2009

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
09/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,396	SANTI ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 30, 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-5, 8-15, 69-74, 76, 79-89 and 91-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 8-15, 69-74, 76, 79-89 and 91-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 30, 2009 has been entered.

Claim Disposition

2. Claims 1, 3-5, 8-15, 69-74, 76, 79-89 and 91-95 are pending and are under examination.

New-Claim Objection

3. The claims 1, 3-5, 8-15, 69-76, 79-89 and 91-95 are objected to because of the following informalities:

Claims 1, 3-5, 8-15, 69-76, 79-89 and 91-95 are objected to because the claims recite non-elected subject matter.

For clarity and precision of claim language it is suggested that claim 8 is amended to read, "A vector comprising the synthetic gene of claim 1.

For clarity and precision of claim language it is suggested that claim 10 is amended to read, "A library of vectors each comprising the synthetic gene of claim 1.

For clarity it is suggested that claim 12 is amended to read, " A cell transformed with the expression vector of claim 9.

For clarity and precision of claim language it is suggested that claim 15 is amended to read, "A method of making a polyketide comprising culturing the cell of claim 14 under conditions in which a polyketide is produced, wherein the polyketide would not be produced by said cell in the absence of said vector".

Claim 76 is objected to because the claim represents an improper product by process claim.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 71 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim recites added material, which is not supported by the original disclosure. Claim 71 recites "less than about 70% sequence identity" and no support was found in the instant specification for this language. Moreover, this language is open and is not limited to the 74-76% exemplified in the instant specification (see Tables 17A and 14A). As the language encompasses, for example 50%, 40%, 10% etc., this language introduces new matter into the claims. Therefore, the specification lacks adequate written description.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 8-10, 12-15, 69-76, 79-89 and 91-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas,

etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966."Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers,* 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents" of the University of California v. Eli Lilly & Co.,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must

describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli,* the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli,* 872, F.2d at 1012, 10 USPQ2d at 1618. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for *a prima facie* case is discussed below.

Further, to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: a) the scope of the invention; b) actual reduction to practice; c) disclosure of drawings or structural chemical formulas; d) relevant identifying characteristics including complete structure, partial structure, physical and/or

chemical properties, and structure/function correlation; e) method of making the claimed compounds; f) level of skill and knowledge in the art; and g) predictability in the art.

The claimed invention is directed to a synthetic gene encoding a polypeptide segment that corresponds to a reference polypeptide segment (see for example claim 1), such as an erythromycin PKS, however, the claims are drawn to “any polypeptide segment” from the listing provided in for example claim 1. Claim 1 also sets forth items (a-d) and indicate for example that the polypeptide segment can have at least 50 amino acids (which are not required to be contiguous, see also claim 86), can have 95% sequence identity to a polypeptide segment encoded by a natural gene, can be encoded by a gene less than 90% identical in nucleotide sequence to the naturally occurring gene and still retain the activity of the naturally occurring product. The language in claim 1 for example, does not set forth a specific segment that would have all or a combination of items (a-d). The "reference polypeptide" in claim 1 is devoid of a structure, especially in view of the recited sequence identity language. The “reference polypeptide segment” of the claimed invention is also devoid of a structure. It is noted that claim 92 recites sequences, however, the claimed invention encompasses for example, any 50-mer from SEQ ID NO:31or 32 recited in the claim and it can be vastly different from the native structure. These structures are very large and 50-mer any where in said structure may not have activity. The claims do not require a full-length PKS polypeptide or a segment comprising a domain. The instant specification at paragraph [0072] sets forth that “as used herein, the term ‘polypeptide segment’ can be

used to refer to a polypeptide sequence of interest. A polypeptide segment can correspond to a naturally occurring polypeptide (e.g., the product of the DEBS ORF 1 gene), to a fragment or region of a naturally occurring polypeptide (e.g., a DEBS module 1, the KS domain of DEBS module 1, linkers, functionally defined regions, and arbitrarily defined regions not corresponding to any particular function or structure), or a synthetic polypeptide not necessarily corresponding to a naturally occurring polypeptide or region. A 'polypeptide segment-encoding sequence' can be the portion of a nucleotide sequence (either in isolated form or contained within a longer nucleotide sequence) that encodes a polypeptide segment (for example, a nucleotide sequence encoding a DEBS1 KS domain); the polypeptide segment can be contained in a larger polypeptide or an entire polypeptide. In general, the term 'polypeptide segment-encoding sequence' is intended to encompass any polypeptide-encoding nucleotide sequence that can be made using the methods of the present invention" (emphasis added). Thus, the claimed invention encompasses a vast amount of variability and is not adequately described.

In addition, no functional limitation is recited in the claims for the recited "polypeptide segment" described as being less than 90% for example. Table 17A of the instant specification discloses 74% and 75% sequence identity and Table 14A shows 76% sequence identity, however the claims broadly recite less than 90% which encompasses a large amount of segments not adequately described. Claim 71 for example recites, "less than about 70% sequence identity at the gene level" and claim 72, recites 1,000-10,000 nucleotides" which means in a structure of 10,000 nucleotides as much 3,000 or more nucleotides could be varied any where in the structure.

It is noted that claim 1 recites a 'PKS polypeptide segment, however, there is no indicia as to what said segment looks like or the reference structure. Thus, the claims encompass a large variable genus, not adequately described. The skilled artisan cannot envision the detailed chemical structure of the genus encompassed in the claims, thus the claimed invention lacks adequate written description. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus could include non-functional proteins or proteins with a different function than the one contemplated. Therefore, the genus of claimed polypeptides encompasses widely variant species. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional. Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d*

1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of genes and the encoded polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1, 3-5, 8-15, 69-74, 76, 79-89 and 91-95 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claims 1, 69-71, 79, 85-89, 91, 93, 94, 95 and the dependent claims hereto are indefinite for the recitation of "a polypeptide segment that corresponds to a reference polypeptide", as it is unclear what "reference polypeptide is being referred to because no structure is recited in the claims, especially in view of the recited percent identity. For instance, 95% identical to what structure?

Claim 13 is indefinite for the recitation of "The cell of claim 12 comprising a polypeptide encoded by the vector of claim 9", because the independent claim is directed to "a polypeptide segment", thus there's no nexus between the claims. See also claim 14.

Claims 86 and 88 lack clear antecedent basis for the recitation of the following, respectively,

"A synthetic gene produced by a process comprising a) obtaining **the DNA sequence** of a naturally occurring gene;

b) obtaining a first amino acid sequence of at least 100 amino acids encoded by **the naturally occurring polyketide synth**ase (PKS) gene…" .

"A synthetic gene encoding a protein at least 100 amino

acids in length, produced by a process comprising

a) obtaining **the DNA sequence** of a naturally occurring polyketide synthase (PKS) gene encoding a naturally occurring protein;

b) obtaining **the first amino acid sequence** of the naturally occurring protein; c) designing an artificial DNA that has less than 80% nucleotide identity with the naturally occurring gene and which encodes a polypeptide with at least 95% sequence identity with the naturally occurring protein…".

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

8. Claims 1, 3-5, 8-15, 69-71, 74-75, 77-82, 85-95 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Katz et al. (U.S. Patent No. 6,004,787, December 21, 1999) in view of Kim et al. (Gene, vol. 199, pages 293-301, 1997).

Katz et al. teach a method to produce novel polyketide structures by designing and introducing specified changes in the DNA governing the synthesis of the polyketide accomplished by introducing one or more specified changes into the DNA sequence. The method of Katz et al. is disclosed as most useful when the segment of the chromosome modified is involved in polyketide biosynthesis, particularly for manipulation of polyketide synthase genes (derived from *erythromycin*), see columns 2-3 of the patent. Katz et al. also teach PKS domains such as AT and ACP, and teach PKS modules (see column 3 of the patent). The method of Katz et al. utilizes restriction enzymes such as SphI and PstI (paragraph [0064] of the patent). Katz et al. discloses a gene cluster 6-deoxyerythronolide from *S. erythraea* (see paragraph 172 of the

patent), which has a native thioesterase II. Katz et al. renders obvious claims directed to vectors and host cells since expression vectors and cells are used in the patent (see paragraph [0017]). Katz et al. also render obvious claims reciting a synthetic gene with a certain percent identity to the encoding gene since following manipulation of the DNA structure the gene of Katz et al. would not be 100% identical to the native structure. Claims reciting a length of at least 100 amino acid residues is also obvious since the phrase "at least" has no upper boundary and the structure of the encoding genes are well established in the art. The recitation of a gene that comprises 500 to 50,000 base pairs is obvious since the gene of Katz et al. falls within that range (see the sequence listing in the patent).

Katz et al. disclose variations and modifications of the methods for obtaining the desired plasmids, hosts for cloning and choices of vectors and segments of *eryA* DNA to clone and modify, that result in substantially the same strains and same products as those described herein. For example, the use of the plasmids pWH3 and pWHM4 as *E. coli-Sac. erythraea* shuttle vectors. In addition, Katz et al. discloses other vectors can be employed wherein all or part of pWHM3 or pWHM4 is replaced by other DNA segments that function in a similar manner, such as replacing the pUC19 component of pWHM3 and pWHM4 with pBR322, available from BRL, employing different segments of the pIJ101 or pJV1 replicons in pWHM3 and pWHM4, respectively, or employing selectable markers other than thiostrepton- and ampicillin-resistance. This disclosure renders claim 10 as obvious since the art recognizes that a library includes a population of vectors having different/heterologous nucleic acids. Claims such as claim 88 are obvious

especially in view of the product by process nature of the claim, since Katz et al. teach the claimed synthetic gene and the recited length has no upper limit. Further, the manipulation of the gene by Katz et al. renders the gene as "synthetic". In addition, claim 76 is also obvious since the aforementioned disclosure in the Katz et al. patent could achieve the recited limitations (see paragraph 176 of Katz et al.). The Katz et al. patent does not explicitly teach codon optimization, however, Kim *et al*. teach that selective codons in a given gene positively correlate with its expression efficiency, (see 293 of the reference). In addition Kim et al. teach the codon optimization of a leader sequence leads to further enhancement of synthetic genes, (see page 297, right column, section 3.3).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a synthetic gene encoding a polypeptide and methods of producing same, that corresponds to a reference polypeptide, wherein said polypeptide is encoded by a naturally occurring PKS gene as recited in claim 1 for example because Katz et al. teach the manipulation of PKS gene structures and Kim et al. teach codon optimization for enhancement of synthetic genes. Furthermore, the instant specification discloses at paragraph [0024] that "[I]n a method for designing a synthetic gene in accordance with the present invention a reference amino acid sequence is provided and reverse translated to a randomized nucleotide sequence which encodes the amino acid sequence using a random selection of codons which, optionally, have been optimized for a codon preference of a host organism. One or more parameters for positions of restriction sites on a sequence of the synthetic gene

are provided and occurrences of one or more selected restriction sites from the randomized nucleotide sequence are removed. One or more selected restriction sites are inserted at selected positions in the randomized nucleotide sequence to generate a sequence of the synthetic gene.

[0039] Identifying positions of preselected restriction sites in the randomized nucleotide sequence, identifying an ability of one or more codons comprising the nucleotide sequence of the restriction site for accepting a substitution in the nucleotide sequence of the restriction site wherein such substitution will (a) remove the restriction site and (b) create a codon encoding an amino acid identical to the codon whose sequence has been changed, and changing the sequence of the restriction site at the identified codon.... [0138] Methods for reverse translation are well known".

Thus, one of ordinary skill in the art would be motivated to produce a synthetic gene with a reasonably expectation of success based on the teachings of Katz et al. because the reference demonstrates the manipulation of gene structures encoding known proteins and Kim et al. as well as the instant specification acknowledges the usage of codon optimization to enhance the expression of a protein of interest. Moreover, the Kim et al. reference is relied upon for the teaching that the expression of a native human gene can be highly optimized by replacing the non- and un-preferred codons with preferred codons. Kim et al. teaches that despite the increased content of CpG dinuclutide in the synthetic gene relative to the wild type human gene, the synthetic gene is expressed at high levels in human cells (see Figure 2 on page 295 of the Kim et al. reference which discloses optimized sequences of the human coding

sequence of the mature human erythropoientin (EPO)). The vast majority of the codon changes resulted in the substitution with G or C leading to increase the content of the CpG pair. Kim et al. teach the expression of the synthetic gene optimized with human preferred codons expressed at higher levels than that optimized with yeast codons (see the paragraph bridging the two columns on page 297). One of ordinary skill in the art would be motivated to combine the teaching of Katz et al. and Kim et al. because Kim et al. teach that since the gene optimized with human codons in human cell expresses at a higher level than that optimized with yeast codons, the ordinary skill in the art would have come to the conclusion that optimizing the signal peptide coding sequence with human codons would enhance the expression even further. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Response to Applicant's Arguments:

9. Applicant's arguments have been fully considered. Withdrawn rejections will not be discussed herein, thus, applicant's comments are moot. A new rejection has been instituted under 35 USC 112 first paragraph, written description pertaining to new matter in the claim language for the reasons set forth above. Note that the rejections under 35 USC 112, first and second paragraphs, and the 103 rejection of record remains.

With regard to the rejection under 35 USC 112, first paragraph, applicant's comments with respect to the written description requirement are noted and to that end

the pertinent sections of the MPEP are cited above that pertain to the instant rejection. Applicant on page 17+ of the response indicates that a person of ordinary skill in the art would be able to understand that the reference polypeptide segment in claim 1 refers to any polypeptide segment of a naturally occurring polyketide synthase which in turn is encoded by a naturally occurring PKS gene. It is further stated that the specification teaches that the amino acid sequences of naturally occurring PKS and the corresponding genes encoding these are known from databases such as BLAST. This argument is not persuasive because the issue at hand is that the claims are to a product that is not adequately described. Claim 1 for example broadly recites any polypeptide segment from for example, erythromycin PKS and there is no guarantee that said segment will be functional, even though the claim recites that function is retained. In fact, the specification in defining the phrase 'polypeptide segment' indicates that polypeptide segment in the instant invention includes, "... arbitrarily defined regions not corresponding to any particular function or structure". Note for example that claim 76 encompasses a portion of the polypeptide segment. The issue is whether a skilled artisan can envision the detailed chemical structure of the product as claimed and whether applicants are in possession of the large variable genus claimed. Applicant state that the claims cannot be read in a vacuum, in deed the claims are being read in light of the instant specification as indicated above.

Applicants opine that incorporating the structure of every reference polypeptide into the claim, as demanded would be equivalent to incorporating the structure of every species into a genus compound claim. The Court of Appeals for the Federal Circuit is

cited as stating that a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. The issue here is not citing all known structures, but citing the claimed structure, the specific synthetic gene of the invention as a reference structure. In deed, a representative amount of species should to be provided for the large genus claimed. Applicant is reminded that the courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966."Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398. "

Clearly, the issue at hand is not to cite all known structures but to describe what the inventor invented in descriptive means using the structure claimed. The claims are directed to a product, and simply recognizes art methodologies to derive similar products is not enough.

Applicants on page 20 of the response indicate that the claims are directed to a gene not the protein *per se*. This argument is not persuasive. The claims as written are directed to 'a synthetic gene encoding a polypeptide segment', not a gene by itself. Thus, the recitation of "a gene encoding a polypeptide segment gives function to said gene and it is therefore, critical to know that the encoded polypeptide segment has function, other said gene would encode a non-functional protein. As per paragraph [0072] of the instant specification a lot of variability is included in the structure of the encoded polypeptide segment which can affect the function of the polypeptide. Furthermore, the specification intends to include in the invention non-functional embodiments and arbitrary structures which are not adequately described (paragraph [0072]).

Applicants also state that the recitation of the language 'the polypeptide retains function' is a functional limitation. This comment is not persuasive as the mere statement is not sufficient, if no function is demonstrated. Applicants state that the function of the natural PKS has been studied. Again the claims are directed to a synthetic structure that varies from the natural structure, thus the issue is not the function of the native structure in the art but the function of the invented product. Applicants conclude that the structure-function correlation is within the expertise of a person of ordinary skill in the art in view of the specification of the application. The MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is

"not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163.

On page 22 of the response applicant's state that "a new method for making synthetic genes encoding polypeptide segments corresponding to those encoded by naturally occurring PKS genes and the synthetic genes made by this method is disclosed. The instant claims are directed to a product not a method and description of the method is insufficient to demonstrate possession of the product. Thus, the rejections remain.

On page 23+, applicants traverse the rejections under 35 USC 112, 2nd paragraph. With regard to the 112, second paragraph rejection, the issue of the recited percent language absent a reference structure remains. Applicants did not amend the claims and the arguments presented are not persuasive since it is unclear what structure the claimed structure is identical to. It is understood that for example the amino acid structure can have the art recognized 20 naturally occurring amino acids however, the composition and arrangement of the 20 can vary, and thus a reference sequence is needed. It is also recognized that possession of the amino acid structure can give you the sequence of the encoding DNA or possession of the DNA structure can give you the amino acids encoded thereby, however, the recitation of a polypeptide encoding segment from a known gene that is very large, does not give a glimpse of a structure because it is unclear what segment is claimed. Note that new grounds of rejections have been instituted under this statue for the reasons stated above.

Applicant traverses the art rejection of record under 35 USC 103 stating that sweeping generalizations are made and that the primary reference Katz does not teach the limitations of the claims. It is further stated that there is no motivation to combine the references. Applicant's arguments have been considered in full, however are not persuasive. The claims are given the broadest reasonable interpretation and the 103 statute only requires a mere teaching or suggestion. Applicant discusses each reference individually, however, the combined teaching of the references renders the claimed invention as obvious. Applicant's statements are not persuasive because Katz combined with Kim discloses polyketides and methods of making same by designing and introducing specified changes in the DNA governing the synthesis of the polyketide accomplished by introducing one or more specified changes into the DNA sequence. The instant claims are product claims not method claims, thus whether the art method differs from the instant application method is not germane to the patentability of the claims. It is recognized that there are some product by process claims in the instant application, however, the issue at hand is that the instant product is obvious over the cited references. Moreover, the instant claims are very broad and do not exclude a product made *in vivo* as stated by applicants. The combined teaching of Katz and Kim discloses PKS genes from *erythromycin,* PKS domains such as AT and ACP, teaches PKS modules, utilizes restriction enzymes such as SphI and PstI, thus the claimed limitations are addressed. As stated above, the manipulation of the gene with the introduction of specified changes in the DNA governing the synthesis of the PKS as disclosed by Katz, an ordinary skilled artisan would know that making said changes

would mean the structures are no longer a 100% identical. Again the claims broadly read on a wide variety of percentages with the "at least language" and the "about language". Further, Applicant's have already stated on the record that the erythromycin gene structure is known in the art. With regard to the recited "free from at least one Type IIS enzyme restriction site", there is no evidence that the gene of the cited Katz reference has the Type IIS restriction site present. Thus, the arguments presented are not persuasive.

Conclusion

10. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Hope A. Robinson/

Primary Examiner, Art Unit 1652